REMARKS

Claims 1-18 are pending in this application. Claims 1-10 have been rejected and claims 11-18 have been withdrawn from further consideration. Claims 1 and 8 have been amended by way of the present amendment. The changes made to these claims are non-narrowing claim amendments directed to matters of 35 U.S.C. §112, second paragraph only. Accordingly, no new matter has been added.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Objection the Abstract of the Disclosure

The Examiner has objected to the Abstract of the Disclosure, since it contains more than one paragraph. Applicants traverse and submit that a new Abstract of the Disclosure has been submitted which contains only a single paragraph. Thus, this objection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Issues Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-10 under 35 U.S.C. §112, second paragraph for the reasons set forth on page 3 of the

outstanding Office Action. Applicants respectfully traverse these rejections.

In claim 1, the Examiner has objected to the recitation of "characterized" as being unconventional claim language. Applicants submit that the recitation of "characterized" has been removed from claim 1, thus, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Second, the Examiner has requested that the word "captur" be corrected to --capture--. Applicants have complied by way of the present amendment. Reconsideration and withdrawal of this rejection are respectfully requested.

Issues Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1 and 8-10 under 35 U.S.C. §103(a) as being obvious over Aoki et al., Clinica Chimica ACTA, December 15, 1988, Vol. 178, No. 2, pages 193-204, in view of Voet et al., Biochemistry 1990. Applicants respectfully traverse.

Aoki relates to an enzyme immunoassay of medullasin in peripheral blood using a bead coated with an anti-medullasin IgG antibody generated in rabbits (refer to pages 195-196 of Aoki). Aoki is concerned simply with measuring amounts of medullasin in the peripheral blood of a patient. Aoki merely discloses that the

amount of medullasin determined by the enzyme immunoassay correlates well with the value calculated with the protease assay measured by the conventional method (See the summary of Aoki, page 193).

In contrast, the present invention has been developed based upon the finding that the medullasin content determined by the immunoassay of Aoki greatly fluctuates. Thus, the amount of variation inherent in this technique is disadvantageous. Accordingly, the present invention lyses the cells prior to the medullasin analysis. This solves the fluctuation problems inherent in the Aoki reference.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify the method of Aoki by incorporating the method of protein isolation taught by Voet. Applicants respectfully disagree with the Examiner. Voet relates to general protein isolation. Voet fails to suggest or disclose the treatment of the present invention for the analysis of medullasin content.

Accordingly, one of ordinary skill in the art is not motivated by either reference to lyse leukocytes prior to determining the amount of medullasin in the patient. Moreover, according to the present invention, the osmotic pressure of the aqueous liquid to

be brought into contact to the blood sample is limited to 250mOsm/kg•H_2O or less, or to 310mOsm/kg•H_2O or more. This osmotic pressure efficiently breaks up the leukocytes to allow the accurate determination of the medullasin content.

The Examiner's attention is drawn to EXAMPLE 2 of the present invention which uses purified water having an osmotic pressure of 0mOsm/kg•H_2O to give variation coefficients of 1.7 and 1.8% for the human medullasin contents in the blood with healthy persons and disseminated sclerosis patients, respectively, as shown in Table 1 (refer to page 2 of the present specification). On the other hand, PBS having an osmotic pressure of around 290mOsm/kg•H_2O produces the results subject to less repeatability, giving a respective variation coefficient of 10.1 and 10.4 (COMPARATIVE EXAMPLE 1).

Voet, which the Examiner asserts renders obvious the lysing step according to the present invention, is completely silent as to the use of an aqueous liquid having an osmotic pressure limited to 250mOsm/kg•H_2O or less, or to 310mOsm/kg•H_2O or more. Accordingly, one is provided with absolutely no motivation based upon the Voet reference to lyse leukocytes prior to quantification of medullasin. Thus, the Examiner has failed to present a valid *prima facie* case of obviousness.

Applicants further point out that Aoki teaches a non-lysing method which claimed to give the result which is well correlated with the values calculated from the protease activity measured by conventional methods. Accordingly, Aoki specifically teaches away from the lysing treatment of the present invention, since Aoki believes that a non-lysing method is perfectly suitable.

Lastly, Applicants point out to the Examiner that dependent claim 10 is further distinguished from the references in that it requires the inclusion of at least one anti-human medullasin monoclonal antibody. The prior art is completely silent as to this point.

In summary, the Examiner has failed to present a valid *prima facie* case of obviousness. Accordingly, the rejection based upon Aoki and Voet is incorrect and should be withdrawn.

The Examiner has also rejected claims 2-7 under 35 U.S.C. §103(a) as being obvious over Aoki in view of Voet and Lapicola, USP 4,745,071. Applicants respectfully traverse this rejection.

As pointed out above, major distinctions exist between the present invention and the Aoki and Voet references. The addition of the Lapicola reference does not cure the deficiencies in the Examiner's rejection. That is, the patentability of the present invention remains even in view of the Lapicola reference since, one

of ordinary skill in the art is provided with no motivation to lyse the leukocytes prior to quantification of medullasin.

In summary, Applicants respectfully submit that the present claims define subject matter which is patentable over the prior art. In particular, Applicants have shown that the Aoki, Voet and Lapicola references fail to render the present claims obvious. Accordingly, the Examiner is respectfully requested to withdraw these rejections and allow the currently pending claims.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Craig A. McRobbie (Reg. No. 42,874) at the telephone number of the undersigned below.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition a three (3) month extension of time for filing a response in connection with the present application. The required fee of $920.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with Markings to Show Changes Made

(Rev. 09/26/01)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE ABSTRACT OF THE DISCLOSURE:

Please replace the Abstract of the Disclosure with the rewritten Abstract of the Disclosure located below:

-- ABSTRACT OF THE DISCLOSURE (amended)

There is provided an immunoassay by which the amount of human medullasin present inside granulocytes, which are one leukocyte component in blood, can be determined with high accuracy and with good reproducibility. Also provided is an [An] immunoassay of medullasin, wherein when measuring the medullasin in blood using an anti-human medullasin antibody, the determination of the amount of human medullasin in a blood sample using said anti-human medullasin antibody is carried out after treating the blood sample with an aqueous liquid having a specific osmotic pressure different to the osmotic pressure of blood to completely break up the leukocytes[; and]. Also provided is a method of diagnosing multiple sclerosis characterized in that the human medullasin content of a blood sample is measured using an immunoassay, and the onset of multiple sclerosis and the extent of the disease is diagnosed according to the size of, or changes in, this measured value.--